201-15676A

HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl) phenoxy]-

CAS No. 26741-53-7

Submitted to the US EPA

BY

Crompton Corporation.

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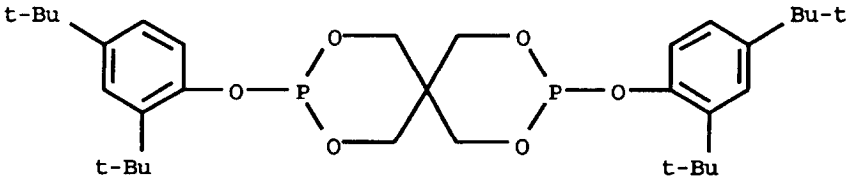
1. General Information

1.1 CAS Number: 26741-53-7

1.2 Molecular Weight: 604.71

1.3 Structure and formula: $C_{33}H_{50}O_6P_2$



1.4 Introduction

2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[2,4-bis(1,1-dimethylethyl) phenoxy]- (Ultranox 626) is used as an antioxidant for polyolefins, polyesters, styrenics, engineering thermoplastics, PVC, elastomers and adhesives. The use of Ultranox 626 is sanctioned by the FDA for food contact applications under 21CFR178.2010 covering antioxidants and/or stabilizers for polymers.

2. Review of Existing Data and Development of Test Plan

Crompton Corporation has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for Ultranox 626.

The availability of the data on the specific SIDS endpoints is summarized in Table 1. Table 1 also shows data gaps that will be filled by additional testing.

Table 1: Available adequate data and proposed testing on Ultranox 626

CAS No. 26741-53-7	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing required?
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y	Y	Y			Y	N
Boiling Point	Y	Y	Y			Y	N
Vapour Pressure	Y				Y	Y	N
Water Solubility	Y				Y	Y	N
Partition Coefficient (Kow)	Y				Y	Y	N
Environmental Fate							
Biodegradation	Y				Y	Y	N
Hydrolysis	N	Y			Y	Y	N
Photodegradation	Y				Y	Y	N
Transport and Distribution between Environmental Compartments	Y				Y	Y	N
Ecotoxicology							
Acute Fish	Y				Y	Y	N
Acute Daphnia	Y				Y	Y	N
Acute Algae	Y				Y	Y	N
Toxicology							
Acute Oral	Y	N	N			Y	N
Repeat Dose toxicity	Y	N	N			Y	N
Genetic toxicity – Gene mutation	Y	N				Y	N
Genetic toxicity – Chromosome aberration	Y	Y	Y			Y	N
Reproductive toxicity	N						N
Developmental toxicity/teratogenicity	Y	N	N			Y	N

A. Evaluation of Existing Physicochemical Data and Proposed Testing

1. Melting Point

The melting point was found to be between 173 – 180°C in a guideline study conducted to GLP.

2. Boiling Point

The boiling point was found to be greater than 311°C in a guideline study conducted to GLP

3. Vapor Pressure

The vapor pressure was estimated to be $2.9x10^{-12}$ hPa at 25°C using MPBPWIN v 1.40.

4. Water Solubility

The water solubility is estimated to be $5.67x10^{-8}$ mg/L at 25°C using WSKOW v 1.40.

5. Partition Coefficient

The Log Pow is estimated to be 10.9 using KOWWIN v 1.66.

Summary of Physicochemical Properties Testing: Existing data for melting point, boiling point, vapour pressure, partition coefficient and water solubility are considered to fill these endpoints adequately.

.Evaluation of Existing Environmental Fate Data and Proposed Testing

1. Biodegradation

The biodegradability of the chemical has been estimated using Biowin v4.00 and the results indicate the chemical to not be readily biodegradable. The chemical contains no biodegradable groups, therefore no biodegradation testing is proposed.

2. Hydrolysis

A GLP study was conducted and it was determined that due to the poor solubility of the test substance in water, a half-life could not be determined. The Fugacity model calculated half-life was 3.6 e003.

3. Photodegradation

The potential for photodegradation of Ultranox 626 has been estimated using the AOPWIN v1.90, and indicated atmospheric oxidation via OH radicals reaction with a half-life of 1.166 hours.

4. Transport and Distribution between Environmental Compartments

An Epiwin Level III Fugacity Model calculation has been conducted Ultranox 626 and indicates distribution mainly to sediment and, to a lesser extent, soil for emissions of 1000 kg/hr simultaneously to air water and soil compartments.

Summary of Environmental Fate Testing: Existing data for photodegradation, hydrolysis, biodegradation and transport and distribution between environmental compartments are considered to fill these endpoints adequately.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

1. Acute Toxicity to Fish

The LC_{50} (96 h) was estimated to be $1.93x10^{-6}$ mg/L using ECOSAR v 0.99g. This is greater than the estimated limit of solubility of the substance.

2. Acute Toxicity to Daphnia

The EC_{50} (48 h) was estimated to be $3.82x10^{-6}$ mg/L using ECOSAR v 0.99g. This is greater than the estimated limit of solubility of the substance.

3. Acute Toxicity to Algae

The EC_{50} (96 h) was estimated to be 3.99x10-6 mg/L using ECOSAR v 0.99g. This is greater than the estimated limit of solubility of the substance.

Summary of Ecotoxicity Testing: Ultranox 626 is estimated to be toxic to the environment only at levels above its limit of solubility. No further testing is proposed.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

The acute oral toxicity of Ultranox 626 is reported as LD_{50} = 5580 mg/kg bw in a rat study. In a study conducted using Leghorn hens, an LD_{50} of >6080 mg/kg bw was reported.

2. Acute Inhalation Toxicity (non-SIDS endpoint)

An LC_{50} of >2000 mg/m^3 was reported in rats after a 1-hour exposure to Ultranox 626.

3. Acute Dermal Toxicity (non-SIDS endpoint)

Acute dermal toxicity was reported as LD_{50} > 2000 mg/kg using rabbits in an OECD 402 study conducted to GLP.

4. Acute I.P. Toxicity (non-SIDS endpoint)

An LD_{50} (mouse) of 14.1 – 20.2 mg/kg is reported in the literature.

5. Skin Irritation (non-SIDS endpoint)

Ultranox 626 was found to be corrosive to rabbit skin in a study conducted to 16CFR 1500.42.

6. Sensitization (non-SIDS endpoint)

The substance was not sensitizing (0/10 sensitization rate) to guinea pigs in a study conducted to OECD 406 under GLP.

7. Repeat Dose Toxicity

In a 90-day oral feed study conducted using rats, the observed NOAEL was 300 ppm (22-26 mg/kg/ bw). Microscopic lesions seen in the livers and spleens of female rats in the 1000 ppm (78-91 mg/kg/day) group were considered to be substance related.

In a 4-month oral dose study conducted using dogs a NOAEL of 12 mg/kg b.w. was reported. Seven out of 8 dogs dosed at 40 mg/kg b.w. displayed degenerative myelin lesions, which were considered to be dose-related.

In a 2-year oral feed study using rats, a NOAEL of 500 ppm (highest dose tested) was reported. No effects were seen at any of the dose levels used.

8. Genotoxicity

Ultranox 626 tested negative in an Ames test using *Salmonella typhimurium* strains TA97, TA98, TA100 and TA102 and *Escherichia coli* strain WP2 (PKM101) with and without metabolic activation.

In a chromosome aberration test (OECD 473) the substance tested positive without metabolic activation using Arochlor 1254-induced rat liver S9.

In an in vivo mouse micronucleus assay (OECD 474) no genotoxic effects were observed.

9. Reproductive and Developmental Toxicity

Female rabbits were dosed orally at up to 200 mg/kg b.w./day with the substance on days 16-18 of gestation and the fetuses removed for examination on day 29 of gestation. No maternal effects were noted in any dose group. 3/15 rabbits miscarried in the high dose group, however the study authors considered this result to be only bordering significance. The number of implantations and the number and weight of the fetuses were not significantly different from the control values. There was no difference in the distribution between male and female fetuses and there were not significant numbers of malformations observed.

Reproductive organs were examined in the 2-year oral feed study in rats described in section 7 above. No greater frequency of anomalies was observed in treated rats compared to controls. In the interests of animal welfare, it is considered to be unnecessary to conduct a separate reproductive toxicity study based on the evidence available from the developmental toxicity study and the 2-year repeat dose study.

Summary of Human Health Effects Testing: All endpoints are considered to have been filled adequately.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance [2] and the systematic approach described by Klimisch et al [3]. These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation [4]. The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. References

[1] US EPA, EPI Suite Software, 2000

[2] USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

[3] Klimisch, H.-J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25:1-5

[4] USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.